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European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
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(54) Title: METHODS AND COMPOSITIONS FOR GENERATION OF MULTIPLE COPIES OF NUCLEIC ACID SEQUENCES AND METHODS OF DETECTION THEREOF

(57) Abstract: The present invention provides novel isothermal methods of generating multiple copies of, detecting and/or quantifying nucleic acid sequences of interest based on limited primer extension or attachment of oligonucleotide pairs using composite RNA/DNA primers. Methods for generating multiple copies of and/or detecting and/or quantifying nucleic acid sequences, wherein products of primer extension or attachment of oligonucleotide pairs comprising a cleavable portion are generated, and wherein cleavage of the products results in dissociation of cleaved products from target polynucleotides, are provided. The invention further provides compositions, kits and systems for practicing these methods.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US 01/47775

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 824 517 A (CLEUZIAT PHILIPPE ET AL) 20 October 1998 (1998-10-20) the whole document	1-173
X,P	WO 01 20035 A (KURN NURITH ;NUGEN TECHNOLOGIES INC (US)) 22 March 2001 (2001-03-22) cited in the application the whole document	1-173
E	WO 02 00938 A (NUGEN TGECHNOLOGIES INC ;KURN NURITH (US)) 3 January 2002 (2002-01-03) the whole document	1-173

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

27 January 2003

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03/02/2003

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/47775

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 174-185
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 174-185

Present claims 174-185 relate to kits and mixtures comprising an extremely large number of possible compounds (primers, target polynucleotides, etc.). In fact, the claims contain so many options and variables, that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-15,32-55,82-96,113-136,168-171

The subject-matter of said claims is directed to a method of generating multiple copies of a nucleic acid sequence of interest involving the use of one composite primer.

2. Claims: 16-31,56-81,97-112,137-167,172-173

The subject-matter of said claims is directed to a different method of generating multiple copies of a nucleic acid sequence of interest involving the use of two primers, wherein at least one primer is a composite primer.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/47775

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5824517	A	20-10-1998	FR 2737223 A1	31-01-1997
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